REMARKS

By the foregoing amendment, claims 1-3 and 8 have been canceled, claim 9 has been amended, and claim 10 has been newly added. Applicants submit that no new matter has been added. Support for the amendment to claim 9 can be found throughout the specification, e.g., on page 13, line 10 through page 14, line 8; and page 20, lines 7-10. Support for newly added claim 10 can also be found throughout the specification, e.g., on page 4, lines 8-11. Entry of the above amendment is respectfully requested.

Information Disclosure Statement

Applicants thank the Examiner for acknowledging receipt of the Information Disclosure Statement filed June 27, 2008, and for returning initialed copies of the Form PTO-1449 submitted therein. Furthermore, Applicants note that a second Supplemental Information Disclosure Statement is being filed concurrently herewith.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Office Action rejects claims 1-3 and 8 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the Office Action alleges that the claims are indefinite because "they recite both a composition and method steps and it is not clear whether the claim is drawn to a composition or to a method of treatment or preventing ischemia [sic] in a mammal" (see Office Action mailed October 17, 2008 on page 4, section 10).

In response, and without acquiescing to the propriety of the instant rejection, Applicants submit that the present amendment is responsive to the rejection under 35 U.S.C. § 112, second paragraph.

Claim Rejections – 35 U.S.C. § 103(a)

The Office Action rejects claims 1-3 and 8 under 35 U.S.C. 103(a) as allegedly being unpatentable over Kole et al. (*J. Infect. Dis.* **180**:811-820, 1999; hereinafter "KOLE"), in view of both Sugimoto et al. (U.S. Patent No. 5,759,572; hereinafter "SUGIMOTO"), and Babincova et al. (*Bioelectrochemistry* **55**:17-19, 2002; hereinafter "BABINCOVA").

In response, and without acquiescing to the propriety of the instant rejection, Applicants submit that the present amendment is responsive to the rejection of claims 1-3 and 8 under 35 U.S.C. § 103(a) as unpatentable over KOLE in view of both SUGIMOTO and BABINCOVA.

The Office Action also rejects claims 1-3, 8, and 9 under 35 U.S.C. 103(a) as allegedly being unpatentable over Shimizu et al. (*Bioorganic and Medicinal Chemistry* **11**:1191-1195, 2003; hereinafter "SHIMIZU") in view of Wang et al. (*Clin. Med. J.* **113**:281-285, 2000; hereinafter "WANG"), Hagiwara et al. (*Cancer Research* **53**:687-692, 1993; hereinafter "HAGIWARA"), KOLE, and BABINCOVA.

In particular, the Office alleges that SHIMIZU teaches a method of treating *Leishmania* infestation comprising intraperitoneal administration of a composition comprising oligomannose-coated liposomes and *Leishmania* peptide antigens. The Office Action further states that SHIMIZU teaches the oligosaccharide-coated liposomes as being able to efficiently interact with the mannose receptor on antigen-presenting cells (APCs) followed by the delivery of the antigen to the APCs. The Office further relies on WANG in support of the assertion that macrophages are APCs, and on HAGIWARA in support of the assertion that macrophages represent the major constituent of milky spots in the omentum and mesentery.

The Office Action concedes that SHIMIZU, WANG and HAGIWARA fail to teach treating *Leishmania* with an anti-cancer drug. For this missing feature, the Office relies upon KOLE which allegedly teaches the treatment of *Leishmania* infestation by using mannosylated liposomes loaded with doxorubicin. The Office further alleges that it would have been obvious to one of ordinary skill in the art to modify the method of SHIMIZU by replacing the peptide antigens of SHIMIZU with the doxorubicin of KOLE to achieve the allegedly predictable result of treating *Leishmania* infestation.

In response, Applicants respectfully submit that the claimed invention is not unpatentable over SHIMIZU in view of WANG, HAGIWARA, KOLE and/or BABINCOVA. First, Applicants submit that SHIMIZU and KOLE are directed to treatment of *Leishmania* and not to treatment of cancer. As conceded by the Office, SHIMIZU, WANG and HAGIWARA fail to teach treating *Leishmania* with an anti-cancer drug. As further set forth by the Office, KOLE teaches the treatment of *Leishmania* infestation (emphasis added). Therefore, for at least this reason, the cited documents, either alone or in any reasoned combination, fail to teach the limitations of the claimed invention.

Second, Applicants submit that one of ordinary skill in the art would not have necessarily expected the omentum or mesentery to be the target tissue of a liposome composition for drug delivery. In support thereof, Applicants refer to a report by Ikehara et al. (*Cancer Res.* **66**:8740-8748, 2006; hereinafter "IKEHARA;" see IDS submitted herewith) which describes a novel carbohydrate recognition-based drug delivery and controlled release system. In particular, IKEHARA show the unexpected result that oligomannose-coated liposomes injected into the peritoneal cavity accumulate in the omentum, whereas bare liposomes are deposited in the liver (see page 8477 and Fig. 5B). Moreover, although it is known that macrophages can accumulate

in the milky spots of the omentum (see, e.g., HAGIWARA et al. at page 687, second column, fifth paragraph), the distribution of liposome compositions susceptible to macrophage uptake does not appear to inherently result in accumulation of the liposome composition in the omentum.

Furthermore, Altin et al. (*Methods* **40**:39-52, 2006; hereinafter "ALTIN" – see IDS submitted herewith) disclose that normal liposomes administered to a patient can be taken up by immune cells, including antigen presenting cells (see, e.g. page 40, paragraph bridging first and second columns). In addition ALTIN describes the use of liposomes as adjuvants for vaccines (*Id.*). However, as disclosed in IKEHARA, the use of mannose-coated liposomes results in the delivery of an anti-cancer agent to the greater omentum or mesentery at a degree which is not achieved or expected by the use of a normal liposome.

Third, one of ordinary skill in the art would not have predicted the extent of the anti-cancer effect achieved by the instant invention. In particular, the oligosaccharide coated liposome of the present invention is efficiently taken up by macrophages, and the macrophages accumulate specifically at a target site such as the greater omentum, resulting in a particularly effective anti-cancer treatment. For example, the specification describes the incorporation of mannose-coated liposomes into peritoneal macrophages within one hour of peritoneal cavity administration of the TRITC-labeled BSA-bearing liposomes (Example 2, page 17). This result shows that the uptake of mannose-coated liposomes by macrophages is quit rapid and highly efficient.

Example 4 and Figure 3 also indicate that mannose-coated liposomes encapsulating an anti-cancer agent accumulate at a target site (the greater omentum) after intraperitoneal administration. In particular, Figure 3 shows that 60% or more of the administered anti-cancer

agent is accumulated at a target site. Thus, these data also show that when a mannose-coated liposome compositions are administered intraperitoneally, the encapsulated agent (here an anti-cancer agent) accumulates at a target site.

The high degree of accumulation of the anti-cancer agent at the target site, as well as the high uptake rate and high uptake ratio of mannose-coated liposomes by macrophages, suggests that the anti-cancer agent is taken up by macrophages very efficiently: a desired characteristic for an anti-cancer agent delivery system. Furthermore, since cancer treatment with liposome compositions is a multi-step process comprising incorporation of the anticancer agent into an oligosaccharide coated liposome, then uptake of the liposome into a macrophage, and followed by the delivery of the macrophage to the target site, the high uptake ratio achieved by the instant invention improves the efficiency of drug delivery at an important early step prior to delivery of the anti-cancer agent to the target site.

Applicants further submit that Example 3 of the instant specification describes the accumulation of macrophages at the target site. Applicants further submit that Figure 2 shows the maximum accumulation of mannose-coated liposomes containing a fluorescence-labeled protein within 12 hours of administration, and that this accumulation is maintained for at least 24 hours. The results described in Example 3 and Figure 2 therefore show that liposome-containing macrophages are delivered to and accumulate at the target site rapidly.

In Example 4(2) on pages 19-20 of the specification, gastric cancer cells were transplanted in the peritoneal cavity of a mouse, and oligosaccharide-coated liposomes containing an anti-cancer agent and oligosaccharide-coated liposomes encapsulating magnetic fine particles were administered thereto. Magnetic field irradiation was then carried out 24 hours after liposome administration. After one week, the effect of the anti-cancer agent was

evaluated, and the results are shown in Figures 4-6. In particular, Figure 5 shows tumor reduction of 80% in mice treated with the anti-cancer drug as compared to control mice.

As mentioned above, the oligosaccharide-coated liposome composition of the present invention containing an anti-cancer agent rapidly accumulated in the target site via macrophage uptake. The concentration of anti-cancer agents in the target site was high, and as a result a high therapeutic effect can be achieved. The qualitative and quantitative data shown in Figures 4 through 6 indicate that significant tumor reduction can be achieved. Such a high therapeutic effect would not be predicted by the any of the above-cited documents, either alone or in combination.

Therefore, Applicants respectfully submit that a *prima facie* case of obviousness is not established by the cited art. Even if it is, *arguendo*, Applicants submit that the unexpected results obtained by the present invention are sufficient to overcome any *prima facie* rejection of the claims over SHIMIZU in view of WANG, HAGIWARA, KOLE, and/or BABINCOVA.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully Submitted,
Naoya KOJIMA et al.

Bruce H. Bernstein
Reg. No. 29,027 42,920

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GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191